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C-REACTIVE PROTEIN AND CORONARY CALCIUM SCORE ASSOCIATION IN CORONARY ARTERY DISEASE

Ali Hosseinsabet[(1)], Ahmad Mohebbi[(2)], Alireza Almasi[(3)]

Abstract

BACKGROUND: Both high-sensitivity C-reactive protein (hs-CRP) and spiral computed tomography coronary artery calcium score (CCS) are valid markers of cardiovascular risk. It is unknown whether hs-CRP is a marker of atherosclerotic burden or whether it reflects a process (eg, inflammatory fibrous cap degradation) leading to acute coronary events.

METHOD AND MATERIALS: In a cross-sectional study, we studied association between hs-CRP and coronary calcium score in 143 patients that were candidate for coronary artery bypass grafting (CABG).

RESULTS: In our study, we found no significant association between hs-CRP and CCS in bivariants (P = 0.162) and multivariable (P = 0.062) analysis but in patients that didn't take statins, this association was significant and positive in bivariant (P = 0.001) but in multivariant analysis this association was negative and significant (P = 0.008).

CONCLUSION: hs-CRP was not associated with CCS. The relation between CRP and clinical events might not be related to atherosclerotic burden. Markers of inflammation, like CRP, and indices of atherosclerosis, such as CAC, are likely to provide distinct information regarding cardiovascular risk.

Keywords: coronary calcification, inflammation, risk factors, Multislice spiral CT, h-CRP.

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Introduction

Many evidences suggest that inflammation plays a major role in the development of atherosclerosis and its clinical manifestations.[1,2] In some studies, plasma levels of inflammatory markers, particularly C-reactive protein (CRP), predict myocardial infarction and cardiovascular death.[3-8] However, CRP is associated with many established risk factors, including dyslipidemia, cigarette smoking, hypertension, diabetes and obesity[9-15] and the relation between CRP and coronary artery disease (CAD) has been significant in some studies[16-18] but in the others has not been significant[17,19-27] and even has been significantly negative.[28,29] The extent to which CRP levels predict clinical events depends on the relation of CRP to the burden of underlying atherosclerosis or the milieu leading to plaque rupture and thrombosis and is unknown. As CRP levels predict clinical events, study on the pathophysiology of this relation is of interest to researchers. In contrast to clinical events, an independent association between CRP levels and coronary[19-29] or carotid[27,30-36] atherosclerosis has not been established clearly. Coronary artery calcification (CAC), measured by electron beam tomography (EBT), or spiral computed tomography might be useful in identifying novel risk factors for coronary atherosclerosis in asymptomatic subjects. The amount of CAC at EBT is correlated with the burden of atherosclerosis at both autopsy and coronary angiography,[37,38] and studies suggest that CAC is a predictor of clinical CAD events in both symptomatic[39] and asymptomatic[40,41] subjects. Studies on CAC might permit differentiation of factors associated with coronary atherosclerosis from those related to plaque rupture or thrombosis.

Studies on CRP and CAC in healthy subjects have produced conflicting results. Whereas some found no association between CRP and CAC,[17-29] others have reported a weak relation.[16-18] It is unclear whether

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these conflicting reports reflect the limitations of study design and analysis or real differences in the pathophysiology of CAC, a measure of coronary atherosclerotic burden, and elevated CRP, a marker of inflammation.

Some studies support the concept that CAC scores and plasma CRP levels might provide independent and complementary information regarding the risk of cardiovascular events.[22,42]

Materials and Methods

The study population was 143 patients with coronary artery disease admitted to Shaheed Rajaei Cardiovascular Center, an academic tertiary referral center, since December 2006 to Mars 2007 for coronary artery bypass grafting.

Exclusion criteria: 1- History of myocardial infarction or unstable angina at previous month; 2- Past history of aortic valve replacement or mitral valve replacement; 3- Past history of CABGs or coronary stenting

All study participants were given written informed consent. The protocol was approved by the Research Committee at the Iran University of Medical Science, Tehran. Age, cardiac risk factors including hypertension, dyslipidema, diabetes mellitus, smoking, family history of coronary disease, and drug history were determined by interview (self-reported), and body mass index (BMI) by examination.

Blood sampling was done for measuring lipid profile, creatinine[44-46] and hs-CRP and then samples were frozen at -70°C for four months. hs-CRP was measured via commercial kits (Pars Azmun Co.), by latex immunoturbid assay and by a single laboratory technician blinded to all clinical and radiologic data. Other clinical tests including lipid profile, creatinine, and coronary calcium scoring by 10 slice spiral CT scan (Siemens Somatom Sensation 10) was done. Calcium score of coronary artery expressed according to Agston et al work[43] that previously explained. A total CAC score was determined from the sum of individual scores of the 4 major epicardial coronary arteries. All scans were interpreted by a single radiologist blinded to all clinical and serologic data.

Data were analyzed by SPSSv15/Win and reported as, mean ± SD if continuous, and as proportions if categorical. Because some variables were not normal distributed, we transformed them to logarithmic for normalization of data and because some patients have CCS = 0, log (CCS + 1) was substituted. Firstly, we assessed association between coronary calcium score [log CCS + 1] and log (hs-CRP) overall by Pearson correlation coefficient and then bivariant in presence of any risk factors, any drug usage and in both sex by this method. Because almost all patients used aspirin and beta blockers, and neglectable percents of patients used calcium channel blockers or gemfibrozil, we did not enter them in our analysis. Secondly, we assessed this correlation by multivariable enter linear regression in overall and then in men and women and then according to statin usage. We entered age, BMI, drug history, all risk factors, lipid profile and creatinine in multivariable analysis.

Results

Table 1 shows demographic characteristics, CRP levels, and CCS scores in the subjects (n = 143).

Bivariant analysis of CRP and CCS in all patients and subgroups are presented in table 2. This correlation was not significant in all of the patients (r = -0.118, P = 0.162). In 60-69 years old patients (r = 0.327, P = 0.031) and in patients were not on statins (r = 0.442, P = 0.001), this correlations were moderate and significant. In other subgroups this correlation was not significant.

Factors that were associated with CCS, when C - reactive protein is not included in fully adjusted, multivariable linear regression are shown in Table 3. Age, male sex and family history of coronary artery disease were positive predictors of CCS.

Table 1. Characteristics of the study sample

Age, year	57.7 ± 9.4
<50	18.2
50-59	39.2
60-69	30.8
>70	11.9
BMI, Kg/m^2	27.2 ± 3.5
<24.99	29.4
25-29.99	49
>30	21.6
TG, mg/dl	153.6 ± 78.2
Cholesterol, mg/dl	171.4 ± 48.8
LDL, mg/dl	94.0 ±31.4
HDL, mg/dl	41.0 ± 37.9
CR, mg/dl	1.37 ± 0.95
hs-CRP, mg/dl	2.89 ± 3.43
CCS	366.4 ± 586.7
Male	74.1
HTN	32.2
DLP	45.5
DM	32.9
C/S	35
FH	14
ACEI/ARB	51.7
Statins	62.2

*Values are mean ± SD, or percent.

†(BMI = Body Mass Index, TG = Triglyceride, LDL = Low Density Lipoprotein, HDL = High Density Lipoprotein, CR = CReatinine , hs-CRP = high sensitive CRP, CCS = Coronary Calcium Score, HTN = Hypertension, DLP = Dyslipidemia, DM = Diabetes Mellitus, C/S = Cigarette Smoking, FH = Family History of coronary artery disease, ACEI/ARB = Angiotensin Converting Enzyme Inhibitor/ Angiotensin Receptor Blocker)

Table 2. Correlation of log(hs-CRP) and log (CCS+1) in all cases and subgroups

GROUP	r	P
MALE	0.122	0.213
FEMALE	0.037	0.828
HTN(+)	0.144	0.339
HTN(-)	0.118	0.248
DLP(+)	0.091	0.469
DLP(-)	0.136	0.236
DM(+)	0.176	0.236
DM(-)	0.096	0.353
FH(+)	0.101	0.673
FH(-)	0.101	0.267
C/S(+)	0.144	0.318
C/S(-)	0.110	0.296
ACEI/ARB(+)	0.091	0.442
ACEI/ARB(-)	0.132	0.281
STATIN(+)	0.006	0.958
STATIN(-)	0.442	0.001
Age <50	0.140	0.944
50-59	0.110	0.420
60-69	0.327	0.031
>70	0.333	0.192
BMI <24.99	0.100	0.528
25-29.99	0.080	0.632
>30	0.323	0.081
ALL CASES	- 0.118	0.162

* (+) is presence the condition and (–) is absence the condition

Table 3. Multivariable Analysis of Factors Associated with Coronary Calcium Score when C - reactive protein is not included in analysis.

	B	SD	P
(Constant)	1.173	1.323	0.377
AGE	0.034	0.008	0.000
SEX	- 0.409	0.191	0.035
HTN	0.304	0.177	0.089
DLP	0.019	0.163	0.909
DM	0.121	0.165	0.464
FH	0.470	0.212	0.028
C/S	0.058	0.172	0.735
ACEI/ABR	- 0.069	0.153	0.651
STATIN	- 0.146	0.157	0.355
LDL	0.000	0.003	0.859
LogHDL	0.138	0.184	0.455
LogTG	- 0.182	0.159	0.257
LogCR	- 0.134	0.252	0.598
BMI	- 0.014	0.021	0.514

*Results of linear regression (log of (CCS + 1) as the dependent variable) are presented when CRP is not included in analysis, as the change log (CCS + 1) for a specific change in risk factor. Models were adjusted for the following variables; age, sex, history of hypertension, history of dyslipidemia, diabetes mellitus, family history of coronary artery disease, smoking, use of the following medications: statins, ACEI/ARB ,LDL [log LDL], HDL [log HDL] ,TG [log TG] ,CR [log CR], body mass index.

Factors that were associated with CCS, when C-reactive protein is included, in fully adjusted, multivariable linear regression are shown in Table 4. Age was only predictor of CCS in presence of CRP and sex and family history of coronary artery disease were not

Table 4. Multivariable Analysis of Factors Associated with Coronary Calcium Score when C - reactive protein is included in analysis.

	B	SD	P
(Constant)	1.046	1.312	0.427
AGE	0.037	0.008	0.000
SEX	- 0.343	0.193	0.078
HTN	0.293	0.176	0.099
DLP	- 0.005	0.161	0.977
DM	0.141	0.164	0.392
FH	0.395	0.213	0.067
C/S	0.068	0.170	0.688
ACEI/ABR	- 0.032	0.153	0.834
STATIN	- 0.204	0.158	0.200
LDL	0.001	0.003	0.657
LogHDL	0.089	0.184	0.630
LogTG	- 0.169	0.158	0.288
LogCR	- 0.063	0.253	0.802
BMI	- 0.013	0.021	0.542
LogCRP	- 0.115	0.061	0.062

*Results of linear regression (log of (CCS + 1) as the dependent variable) are presented when CRP is included in analysis as the change log (CCS + 1) for a specific change in risk factor. Models were adjusted for the following variables; age, sex, history of hypertension, history of dyslipidemia, diabetes mellitus, family history of coronary artery disease, smoking, use of the following medications: statins, ACEI/ARB ,LDL [log LDL] ,HDL [log HDL] ,TG [log TG] ,CR [log CR], body mass index and CRP [log CRP].

Table 5. Multivariable Analysis of Factors Associated with Coronary Calcium Score C - reactive protein in patients did not use statin

	B	SD	P
(Constant)	3.774	1.682	0.031
AGE	0.021	0.012	0.088
SEX	- 0.653	0.262	0.017
HTN	0.318	0.259	0.227
DLP	0.086	0.243	0.724
DM	0.250	0.226	0.276
FH	0.682	0.318	0.038
C/S	- 0.346	0.275	0.215
ACEI/ABR	0.191	0.231	0.414
LDL	0.004	0.004	0.294
LogHDL	0.188	0.219	0.396
LogTG	- 0.261	0.241	0.285
LogCR	- 0.531	0.292	0.077
BMI	- 0.068	0.037	0.077
LogCRP	- 0.278	0.100	0.008

*Results of linear regression (log of (CCS + 1) as the dependent variable) are presented in patients that not use statin, as the change log (CCS + 1) for a specific change in risk factor. Models were adjusted for the following variables; age, sex, history of hypertension, history of dyslipidemia, diabetes mellitus, family history of coronary artery disease, smoking, use of the following medications: statins, ACEI/ARB ,LDL [log LDL], HDL [log HDL], TG [log TG] ,CR [log CR], body mass index and CRP [log CRP].

predictors of CCS after adjustment for CRP level. Because in bivariants analysis the association of log (CRP) and log (CCS + 1) was significant in patient that were not on statins, we analyzed this association in fully adjusted, multivariable linear regression. Table 5 shows this analysis. Male sex and family history of coronary artery disease are positive predictors of CCS, and CRP was negative predictor of CCS (P = 0.008) in patients that were on statins.

Discussion

CCS, measured at spiral CT, might be useful for identifying novel risk factors and exploring the relation of risk factors with coronary atherosclerosis. We have examined the association between plasma CRP and CCS in patients that were candidate for CABGs. In previous studies subjects were suspected to have coronary artery disease without any documentation but in our study patients had coronary artery disease documented by selective coronary artery angiography. We found no evidence of a positive association between hs-CRP and calcium scores. Indeed these data suggest an inverse relationship between hs-CRP levels and coronary calcium in patients do not take statin. We believe that, lack of a positive association between hs-CRP and coronary calcium score needs careful consideration. The lack of correlation in the current data between spiral CT score and hs-CRP suggests that calcification may be less likely to reflect inflammation per se. Spiral CT detected calcification may predominantly be a marker for mature and hence stable atherosclerotic plaque, and thus only can be an indirect marker for the presence of uncalcified rupture-prone lesions, which may be probable markers for future cardiac events, but correlation between soft, noncalcified plaque and cardiac events was not confirmed.[24] Deposition of calcium in atherosclerotic lesions has been shown to be an active process analogous to the formation of bone spicules.[47] Furthermore, it appears to involve cells of special embryonic lineage.

Therefore coronary calcification may not merely be a direct consequence of atherogenesis but may depend on the presence of specific determinants independent of the central processes involved in plaque formation. The reasons for the lack of association between CRP and CCS, in contrast to a more consistent association between CRP and clinical events, are unclear. However, this finding supports the concept that CRP levels might not be related to atherosclerosis progression, distinct from being a marker of plaque rupture and thrombosis. Therefore, CRP might not be useful in identifying the underlying mechanisms of atherosclerosis initiation or progression. The present findings suggest that the relationship between higher CRP levels and incident cardiovascular events may reflect the composition, morphology, and stability of plaque rather than overall atherosclerotic burden.[48] Because CCS are associated with risk for subsequent cardiovascular events and provide a measure of disease processes distinct from CRP, these two markers may be complementary rather than competitive for risk prediction.[43]

This study, demonstrate that hs-CRP is unrelated to the presence and severity of clinical calcified atherosclerosis and suggests that serologic inflammatory markers are principally a measure of the atheroinflammatory disease process and are not an index of the extent of coronary atherosclerotic plaque. The independent prognostic utility of quantifying calcified atherosclerosis and systemic inflammation suggests that disease and process markers of atherosclerosis may be complementary tools in coronary heart disease prediction.

We used a validated commercial assay for the measurement of hs-CRP, but variability in commercial assays may limit the validity of these data. We used CCS as a surrogate for coronary atherosclerotic plaque burden on the basis of the well-established relationship between CCS and the extent of histologic

plaque.[37] However, atherosclerosis in vascular beds other than the coronary arteries could also contribute to the level of hs-CRP.[49]

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